IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

The Commissioner of Patents & Trademarks
Washington, D.C. 20231
Attn: Box Patent Application

JC685 U.S. PTO
07/19/00

Docket No. **SCH 1686 C1**
Prior Application: SCH 1686
Examiner: Qazi, S.
Art Unit: 1616

JC685 U.S. PTO
09/619493
07/19/00

Sir: This is a request for filing a
■ Continuation
□ Divisional
Under 37 C.F.R. 1.53(b), of prior application Serial No. **09/331,397** filed on **June 21, 1999** of **Norman Nashed**, for **THERAPEUTIC GESTAGENS FOR THE TREATMENT OF PREMENSTRUAL DYSPHORIC DISORDER**

1. ☒ Enclosed are **10** pages of the specification including claims and **0** sheets of drawings.

2. ☒ Enclosed is a copy of the oath or declaration as originally filed in Serial No. **09/331,397** on **June 21, 1999** in accordance with 37 C.F.R. §1.63(d).

3. ☒ The filing fee is calculated below:

FOR	NUMBER FILED	NUMBER EXTRA	RATE	FEE
TOTAL CLAIMS	23 - 20	3	$18	54.00
INDEPENDENT CLAIMS	1 - 3	0	$78	0.00
□ MULTIPLE DEPENDENT CLAIM PRESENTED				
□ Small Entity Status Claimed under 37 CFR 1.9 and 1.27		BASIC FEE		744.00
Statement(s): □ Attached □ Filed in Parent		TOTAL FILING FEE		$744.00

4. ☒ The amount of $ 744.00 is included in the attached check.

☒ If a check is not attached, authorization is given to charge the amount indicated in the above sentence to Deposit Account No. 13-3402; two copies of this page being attached for this purpose.

5. □ Please charge my Deposit Account No. 13-3402 in the amount of $_____, two copies of this sheet are attached.

6. ☒ The Commissioner is hereby authorized to charge any deficiencies or credit any overpayment in payment of the following fees associated with this communication or otherwise due during the pendency of this application to Deposit Account No. 13-3402.
☒ Any filing fees under 37 CFR §1.16 for the presentation of extra claims.
☒ Any patent application processing fees under 37 CFR §1.17.

7. □ Cancel in this application original claims _____ of the prior application before calculating the filing fee.

8. ☒ Amend the specification by inserting before the first line the sentence:
-- This is a ■ continuation, □ divisional, of application Serial No. **09/331,397** filed **June 21, 1999** .--

9. ☒ Priority of application No. **196 54 609.5** filed on **December 20, 1996** in **Germany** is claimed under 35 U.S.C. §119.

10. ☒ The certified copies have been filed in prior application Serial No. **09/331,397** filed **June 21, 1999** .

11. ☒ The prior application is assigned of record to **SCHERING AKTIENGESELLSCHAFT** .

12. ☒ The power of attorney in the prior application is to: J. William Millen (19,544); John L. White (17,746); Anthony J. Zelano (27,969); Alan E.J. Branigan (20,565); John R. Moses (24,983); Harry B Shubin (32,004); Brion P. Heaney (32,542); Diana Hamlet-King (33,302); Richard J. Traverso (30,595); Richard E. Kurtz (33,936); John A. Sopp (33,103); John H. Thomas (33,460); Richard M. Lebovitz (37,067) and Luan C. Do (38,434)
☒ a. The power appears in the original papers in the prior application.
☒ b. Address all future communications to MILLEN, WHITE, ZELANO & BRANIGAN, P.C.

13. □ A preliminary amendment is enclosed.

14. □ An Information Disclosure Statement is enclosed.

15. ☒ Incorporation By Reference.
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 2, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

Date: July 19, 2000

Nancy J. Axelrod

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
Norman NASHED	:	Examiner: NOT YET ASSIGNED
Application of Parent Serial No.: 09/331,397	:	Group Art Unit: NOT YET ASSIGNED
Filed: July 19, 2000	:	

For: **THERAPEUTIC GESTAGENS FOR THE TREATMENT OF PREMENSTRUAL DYSPHORIC DISORDER**

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D. C. 20231

Sir:

Prior to examination, please amend the accompanying application as follows.

IN THE ABSTRACT:

Please delete the Abstract of the Disclosure in its entirety, and substitute therefor the Abstract which appears on a separate sheet attached hereto.

IN THE CLAIMS:

In the title, change "Claims" to --We claim:--

Please amend the claims as follows:

1. (Amended) [Use of a therapeutic gestagen for the production of a pharmaceutical agent for the treatment of] A method of treating premenstrual dysphoric disorder [(PMDD)], comprising administering to a patient in need of such treatment a therapeutically effective amount of gestagen.

2. (Amended) [Use of] The method of claim 1, wherein the gestagen is drospirenone, cyproterone acetate, or dienogest [according to claim 1].

3. (Amended) [Use according to] The method of claim 1, further comprising administering [together with] an estrogen.

4. (Amended) [Use according to] The method of claim 3, wherein the estrogen is [together with a]synthetic [estrogen].

5. (Amended) [Use according to] The method of claim 4, [together with] wherein the estrogen is ethinylestradiol.

6. (Amended) [Use according to] The method of claim 3, [together with] wherein the estrogen is an estrogen sulfamate.

7. (Amended) [Use according to] The method of claim 3, [together with a] wherein the estrogen is natural [estrogen].

8. (Amended) [Use according to] The method of claim 7, [together with] wherein the estrogen is estradiol, estradiol valerate or another estradiol ester.

9. (Amended) [Use according to] The method of claim 1, wherein the gestagen is adminstered only during the luteal phase of the female menstrual cycle.

10. (Amended) [Use according to] The method of claim 9, wherein the gestagen is administered from day 10 to 28 of the menstrual cycle.

11. (Amended) [Use of] The method of claim 1, wherein the gestagen is [according to claim 1] drospirenone, and it is administered in an amount of 0.5 mg to less than 5 mg daily.

12. (Amended) [Use of ethinylestradiol according to] The method of claim 5, wherein the ethinylestradiol is administered in an amount of 0.010 to 0.05 mg daily.

13. (Amended) [Use of estradiol according to] The method of claim 8, wherein estradiol is administered in an amount of 1.0 [g] to 3.0 mg daily.

Please add the following new claims:

--14. The method of claim 2, wherein the gestagen is drospirenone.

15. The method of claim 3, wherein the gestagen and estrogen are administered together.

16. The method of claim 15, wherein the gestagen and estrogen are administered orally.

17. The method of claim 8, wherein the estrogen is estradiol.

18. The method of claim 11, wherein the daily dose of drospirenone is 1.0 to 4.0 mg.

19. The method of claim 4, wherein the estrogen is an estratrien-3-amidosulfonate.

20. The method of claim 4, wherein the estrogen is a 14a, 15a-methylene steriod from the estrane series.

21. The method of claim 3, wherein the gestagen and estrogen are administered continuously.

22. The method of claim 3, wherein the gestagen and estrogen are administered sequentially.

23. The method of claim 3, wherein the gestagen and estrogen are administered cyclically.--

REMARKS

Claims 1-13 have been amended to place them in a form more customary for U.S. practice, thereby obviating the rejection over 35 USC 101. Newly added claims 14-23 recite embodiments of the invention and are fully supported by the specification.

Respectfully submitted,

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Therapeutic Gestagens for the Treatment of Premenstrual Dysphoric Disorder

This invention relates to the use of therapeutic gestagens for the treatment of premenstrual dysphoric disorder (PMDD).

An accurate diagnosis and an effective treatment are essential to treat or to mitigate this disorder. The diagnosis is confirmed only in about 25% of women who report PMDD, when the symptoms are observed over another cycle. The most important symptoms are a state of emotional stress, irritability, unease and the feeling of being out of control. The first occurrence of PMDD is usually in one's late 20s, although it doesn't usually occur in patients until their mid-30s.

PMDD manifests itself by the occurrence of at least 5 of the 11 symptoms that are listed below; the latter must occur to a serious extent premenstrually and lessen postmenstrually. These 5 symptoms must comprise at least one dysphoric symptom (irritability, mood swings, anxiety conditions or depression). Several physical symptoms are counted as one symptom.

Criteria for the Existence of Premenstrual Dysphoric Disorder

In the prospective evaluation by recording the symptoms of the patient over 2 or 3 menstrual cycles, 5 (or more) of the symptoms that are listed below occur during the last week of the luteal phase, but no longer occur postmenstrually. At least one of the symptoms must be the first, second, third or fourth

symptom below.

1. Noticeably stressed mental state, feelings of hopelessness or self-doubt
2. Noticeable feeling of anxiety, tension, feeling of "being on the edge"
3. Noticeable emotional tendencies (e.g., suddenly feeling sad or fretful or increased sensitivity to rejection)
4. Lasting and noticeable feelings of unease or irritability or increased interpersonal conflicts
5. Decreasing interest in conventional activities (e.g., work, school, friends, hobbies)
6. Subjective sensation of concentration difficulties
7. Lethargy, slight exhaustion or noticeable lack of energy
8. Noticeable change in appetite, overeating or special food cravings
9. Hypersomnia or insomnia
10. Subjective feeling of being overwhelmed or out of control
11. Other physical symptoms, such as breast tenseness or swelling, headaches, joint or muscle pains, floating sensation, weight gain.

The listed disorders must have noticeably adverse effects wtih respect to work or school or conventional social activities and relationships to others. The disorders must not be an aggravation of the symptoms of other disorders (e.g., greater

depressive disorder, panic disorder, dysthymic disorder, personality disorder).

Otherwise, reference is also made to the DSM-IV, American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Washington, DC, America Psychiatric Association, 1994, p. 715 ff, "Premenstrual Dysphoric Disorder."

Since the symptoms of PMDD seem to be associated with the progesterone cycle, the hope was that hormonal therapies could be helpful to the treatment of PMDD. This hope has not been confirmed. Hormone therapies lead only to mixed results. Hormone antagonists are more likely indicated for the treatment of somatic symptoms of the premenstrual symptom (PMS) than PMDD.

To date, selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetines, sertralines) and other psychotropic active ingredients (e.g., alprazolam) are considered as most effective for symptomatic treatment of PMDD.

A treatment with these compounds can cause serious side effects; in addition, only a portion of the symptoms that constitute the PMDD image of disease can be mitigated with psychotropic active ingredients.

The object of this invention is to indicate an effective pharmaceutical agent for the treatment of PMDD, which avoids the drawbacks of pharmaceutical agents used to date.

It has been found that therapeutic gestagens can be used for the production of medications for the treatment of PMDD. This is

very surprising, since hormonal treatments had already been considered but had not turned out to be helpful.

Therapeutic gestagens are defined as those gestagens that in addition to their gestagenic action have a partial profile that is advantageous for therapeutic purposes, i.e., that additionally exert an antiandrogenic action and optionally also an anti-mineral-corticoidal action. This additional action must occur as early as at a dosage at which a gestagenic effect also occurs.

Examples of such therapeutic gestagens that are to be used according to the invention are cyproterone acetate, dienogest and especially drospirenone. While the first two exhibit gestagenic and antiandrogenic action, drospirenone, like the natural progesterone, has an additional anti-mineral-corticoidal action. In contrast to the natural hormone, it is also bioavailable after oral administration.

The exact history of the origin of PMDD is unknown to date. Both the fluctuation of ovarian steroid hormones and the water retention in the luteal phase of the menstrual cycle demonstrably play a role in PMDD. In this case, it appears to provide interaction between the ovarian steroid hormones and neutrotransmitters, such as, e.g., serotonin.

The symptoms of PMDD are mitigated by the antiandrogenic action of therapeutic gestagens. Increased testosterone levels during the late luteal phase were used to explain the irritative and impulsive form of phenomena that characterize the premenstrual state of PMDD that readily responds to irritants. Testosterone levels, especially in the case of free testosterone,

have a positive correlation with premenstrual irritability (Eriksson, E. et al., Serum Levels of Androgens Are Higher in Women with Premenstrual Irritability and Dysphoria than in Controls, Psychoneuroendocrinology 1992: 17, 195-204).

In addition, improvement of the general mental state (general mood symptoms) is achieved by treatment with a therapeutic gestagen. This must be all the more surprising than only psychotropic active ingredients having been used to date for treatment. This improvement is documented in a "Quality of Life" study.

Based on the anti-mineral-corticoidal properties of the gestagen drospirenone, a reduction of the physical symptoms, such as breast tenseness or swelling, headaches, floating sensation, or weight gain, start with a feeling of tightness through the clothing, shoes or rings.

A pharmaceutical agent according to the invention can contain either a therapeutic gestagen by itself or a therapeutic gestagen in combination with an estrogen. Both natural and synthetic estrogens are suitable as estrogens.

The dosage of the therapeutic gestagens is to be 0.5 mg to less than 5 mg, preferably 1.0 to 4.0 mg per day in the case of drospirenone or an equivalent-action amount of another therapeutic gestagen.

The gestagenic and estrogenic active ingredient components are preferably administered orally together. The daily dose is preferably administered one time.

As estrogens, all natural and synthetic compounds that are known as being estrogenically active are suitable.

As natural estrogens, these are especially estradiol and also its longer-acting esters, such as valerate, etc., or estriol.

Synthetic estrogens, such as ethinylestradiol, 14α,17α-ethano-1,3,5(10)-estratriene-3,17β-diol (WO 88/01275), 14α,17α-ethano-1,3,5(10)-estratriene-3,16α,17β-triol (WO 91/08219) or the 15,15-dialkyl derivatives of estradiol, and of these especially 15,15-dimethylestradiol, can preferably be mentioned. As a synthetic estrogen, ethinylestradiol is preferred.

Also, the estratrien-3-amidosulfonates (WO 96/05216 and WO 96/05217) that are derived from estradiol or ethinylestradiol, that are distinguished by low hepatic estrogeneity and that have become known recently are suitable as estrogens for common use with the compounds of general formula I.

Finally, the 14a,15a-methylene steroids from the estrane series, especially the 14,15a-methylen-17a-estradiol and the corresponding 3-amidosulfonate derivatives can be mentioned.

The estrogen is administered in an amount that corresponds to that of 0.010 to 0.05 mg of ethinylestradiol or 1.0 to 3.0 mg daily.

The formulation of the pharmaceutical preparations based on the new compounds is carried out in a way that is known in the art, by the active ingredient, the therapeutic gestagen, optionally in combination with an estrogen, being processed with the vehicles, diluents, optionally taste correctives, etc., that

are commonly used in galenicals and being converted into the desired form of administration.

For the preferred oral administration, especially tablets, coated tablets, capsules, pills, suspensions or solutions are suitable.

For parenteral administration, especially oily solutions, such as, for example, solutions in sesame oil, castor oil and cottonseed oil, are suitable. To increase solubility, solubilizers, such as, for example, benzyl benzoate or benzyl alcohol, can be added.

The therapeutic gestagen, optionally in combination with an estrogen, can also be administered continuously by an intrauterine release system (IUD); in this case, the release rate of the active compound(s) is selected in such a way that the dose that is released daily lies within the already indicated dosage range.

In the case of a mono-preparation that contains only one therapeutic gestagen, the latter can be created for the administration of daily dosage units over the entire menstrual cycle.

According to a variant of the invention, the pharmaceutical agent for treatment of PMDD is administered only during the luteal phase of the cycle, beginning at the earliest on day 10 until the end of the cycle, usually up to day 28. An extended administration is also conceivable.

If the therapeutic gestagen according to this invention is used in combination preparations together with an estrogen, these

preparations can be provided for continuous, sequential or cyclic administration of active ingredients.

Continuous administration is defined here as the daily common administration of the two active ingredients.

Sequential administration means administration of the therapeutic gestagen starting on day 10 at the earliest until the end of the cycle. Administration from day 10 to 28 is preferably meant here. Together with the gestagen, the estrogen is administered, separately or in the same dosage unit. In addition, the estrogen is administered on a few or all of the gestagen-free days.

Cyclic administration is defined as the administration of the two active ingredients starting from the first day of the cycle until a time before the last day of the cycle, preferably day 21 to day 23.

Based on the ovulation-inhibiting properties of the therapeutic gestagen or the combination preparations of gestagen and estrogen, these preparations are also suitable for contraception, if the active components are contained in amounts that are adequate for this purpose. These preparations are therefore preferably used for symptomatic treatment of women of child-bearing age with average to serious symptoms of PMDD. In this case, the use of the therapeutic gestagen is preferably carried out with a synthetic estrogen, such as ethinylestradiol.

Combination preparations of a therapeutic gestagen with a natural estrogen, especially estradiol, can be used preferably for symptomatic treatment of average to serious symptoms of PMDD

in perimenopausal women. Perimenopause begins with the occurrence of menopausal symptoms and ends one year after menopause, the last menstruation.

In especially serious cases of PMDD, the pharmaceutical agent according to the invention can also be used in connection with a psychotropic medication of the above-mentioned type.

The example below is used for a more detailed explanation of the invention:

Fertile women, who were classified according to the above-indicated criteria 1. to 11. as PMDD patients, are treated orally over at least 4 cycles, in each case from day 1 to day 21 of the cycle daily, with an amount of 3 mg of drospirenone together with 30 µg of ethinylestradiol. Then come 7 pill-free days or 7 daily placebos. After a treatment over 4 to 6 cycles, the symptoms that fall into the category criteria 1. to 11. are carefully evaluated again. In the case of all of the women treated, a significant improvement relative to at least one of the symptoms that occurred before the beginning of the treatment, but not only the 11th symptom, is observed.

Claims

1. Use of a therapeutic gestagen for the production of a pharmaceutical agent for the treatment of premenstrual dysphoric disorder (PMDD).

2. Use of drospirenone, cyproterone acetate, dienogest according to claim 1.

3. Use according to claim 1, together with an estrogen.

4. Use according to claim 3, together with a synthetic estrogen.

5. Use according to claim 4, together with ethinylestradiol.

6. Use according to claim 3, together with an estrogen sulfamate.

7. Use according to claim 3, together with a natural estrogen.

8. Use according to claim 7, together with estradiol, estradiol valerate or another estradiol ester.

9. Use according to claim 1, only during the luteal phase of the female menstrual cycle.

10. Use according to claim 9 from day 10 to 28 of the menstrual cycle.

11. Use of drospirenone according to claim 1 in an amount of 0.5 mg to less than 5 mg daily.

12. Use of ethinylestradiol according to claim 5 in an amount of 0.010 to 0.05 mg daily.

13. Use of estradiol according to claim 8 in an amount of 1.0 g to 3.0 mg daily.

ABSTRACT OF THE DISCLOSURE

A method for treating premenstrual dysphoric disorder comprises administering a therapeutically effective amount of a gestagen. Optionally, a natural or synthetic estrogen is also administered. In one embodiment, the gestagen and optional estrogen are administered during the luteal phase of the female menstrual cycle, preferably from day 10 to day 28.

Docket No.
SCH 1686

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

THERAPEUTIC GESTAGENS FOR THE TREATMENT OF PREMENSTRUAL DYSPHORIC DISORDER

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on **22 December 1997** as United States Application No. or PCT International Application Number **PCT/DE97/03032**

and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
196 54 609.5	**Germany**	**20 December 1996**	☐
(Number)	(Country)	(Day/Month/Year Filed)	
			☐
(Number)	(Country)	(Day/Month/Year Filed)	
			☐
(Number)	(Country)	(Day/Month/Year Filed)	

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

I. William Millen (Reg. No. 19,544)
John L. White (Reg. No. 17,746)
Anthony J. Zelano (Reg. No. 27,969)
Alan E.J. Branigan (Reg. No. 20,565)
John R. Moses (Reg. No. 24,983)
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Brion P. Heaney (Reg. No. 32,542)
Richard J. Traverso (Reg. No. 30,595)
Diana Hamlet-King (Reg. No. 33,302)
John A. Sopp (Reg. No. 33,103)
Richard E. Kurtz (Reg. No. 33,936)
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Sole or first inventor's signature — Date
23. APRIL 1999

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